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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION
09/776,910	02/06/2001	Robyn Joyce Russell	50179-087	3696

7590 05/27/2003

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	15

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,910	RUSSELL ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-29* is/are pending in the application.

4a) Of the above claim(s) *10-12 and 19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/068,960* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 9-29 are still at issue and are present for examination. Claims 9, 13-18 are now under consideration. Claims 10-12, 19-29 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 9, 13-18 in Paper No. 14 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups I-II would not be burdensome on the Examiner. This is not found persuasive because while the searches for the two groups overlap, they are not coextensive. The search for Groups I and II would each require the search of subclasses unnecessary for the search of elected Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-12, 19-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 14. Examiner will consider rejoinder of the two groups when the elected claims are in condition for allowance.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/068960, filed on 5-20-1998.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 is drawn to an enzyme capable of hydrolyzing a organophosphate wherein the enzyme is produced by a cell transformed with a DNA molecule comprising a nucleotide sequence having at least 60% homology with "LcαE7", in which the protein encoded by the DNA differs from "E3" at least in substitution of Trp at position 251. The entire claim is very vague. It is not clear to the Examiner as to what applicants are comparing, whether DNA with DNA or DNA with polypeptide etc. By simply reciting LcαE7 or E3, applicants do not make it clear whether it the DNA or the protein sequence they are comparing. Furthermore, without providing a specific SEQ I D NO: for both LcαE7 and E3 it is impossible for the Examiner to search the claim. Furthermore, reciting abbreviated names such as LcαE7 or E3 also makes no sense as it is not clear as to whether it is the polypeptide or the DNA that applicants are comparing. Examiner urges applicants to expand all abbreviation and provide full names of the enzymes in the all the claims.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 recites the phrase "hybridizes thereto". It is not clear to the Examiner as to what specific hybridization conditions are encompassed in the above phrase. A perusal of the specification doesn't provide a specific definition for the above phrase rendering the above claim indefinite.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18, again uses abbreviations without proper expansions and it is not clear to the Examiner as whether applicants are comparing DNA or polypeptide. Furthermore, as applicants do not provide specific SEQ ID NO in the claims, it is impossible to perform a accurate search.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme encoded by either SEQ ID NO:1, 3, or 5 and having a single amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and capable of hydrolyzing organophosphates, does not reasonably provide enablement for any such enzyme encoded by polynucleotides having at least

60% homology to the above polynucleotides or a sequence that hybridizes thereto. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 9, 13-18 are so broad as to encompass any organophosphate degrading enzyme encoded by polynucleotides having at least 60% homology to the above polynucleotides or a sequence that hybridizes thereto. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of said enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one said enzyme comprising the specific amino acid changes mentioned above. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The

specification is limited to teaching use of polypeptide encoded by SEQ ID NO: 1, 3, and 5 but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any organophosphate hydrolyzing enzyme encoded by polynucleotides that are at least 60% identital to SEQ ID NOS:1, 3, or 5 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of above enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues

with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including enzymes encoded by polynucleotide that are at least 60% identical to SEQ ID NO:1, 3, 5 with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 16, 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 18 is directed to polypeptides capable of degrading organophosphate in which the respective amino acid at position 251 is Ser. The specification does not contain any disclosure of the structure of all polypeptide sequences included in the claimed genera. The genus of polypeptides claimed is a large variable genus with the potentiality of having many different structures. Therefore, many structurally distinct polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is

insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., a Ser at position 251 and that it hybridizes to SEQ ID NO:1, 3, 5,) does not constitute a substantial portion of the genus as the remainder of the structure of polypeptide having activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Whyard (a) et al. (Pesticide Biochemistry and Physiology, 1994, Vol. 50(3):198-206) or Whyard (b)et al. (Biochemical genetics, 1994, Vol. 32(1-2):9-24). This rejection is based upon the public availability of a printed publications. Claims 9, 13-18 are directed to enzyme capable of

hydrolyzing an organophosphate produced recombinantly by a cell transformed with a DNA comprising a nucleotide sequence that is at least 60% identical to DNA encoding a carboxylesterase in the blow fly *L.cuprina* and which encodes such an enzyme in which the original amino acid Trp at position 251 is substituted with a Ser , Leu, ser, Ala, Ile, Val, Thr, Cys, Met or Gly. Whyard (a) and Whyard (b) references disclose the isolation and characterization of malathion carboxylesterases from *L.cuprina* strains that were resistant to the organophosphate insecticide. Because applicants have isolated the cDNA responsible for encoding the malathion carboxylesterase purified and characterized by Whyard et al. from resistant strains of *L.cuprina*, and have not shown any material difference between the enzyme isolated by Whyard et al. and the recombinant form of the enzyme, Examiner takes the position that the enzymes disclosed in the references and that claimed in the instant application are one and the same. With regard to the specific amino acid substitution claimed, Examiner takes the position that applicants have simply sequenced the naturally produced enzyme isolated and characterized by Whyard et al. and found out the specific amino acid change by comparing it with carboxylesterase enzymes produced by non-resistant strains. Therefore, while the above references do not explicitly disclose the amino acid sequence or disclose the method of obtaining the enzyme through recombinant techniques as claimed by the applicants, Examiner takes the position that such characteristics of the enzyme are all inherent and applicants have not done any thing to the naturally produced enzyme except for determination of the amino acid sequence and isolating the corresponding cDNA for transforming a host cell to make recombinant enzyme. Applicants have also not shown any specific characteristic that renders the recombinant enzyme

as a distinct enzyme from the naturally occurring enzyme. Therefore, Whyard (a) or Whyard (b) et al. anticipate claims 9, 13- 18 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

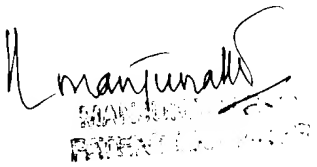
Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
May 24, 2003